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Nasopharyngeal Carcinoma in Children

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Key words: Epstein-Barr virus, cervical lymphadenopathy, epithelial cancers in children

Maria Werner-Wasik, MD (Fellow, Radiation Oncology)

The patient is a 13-year-old Vietnamese boy who first presented in Vietnam 18 months ago with bilateral neck adenopathy, unresponsive to antibiotics. This progressed over the next 5 months to the point of causing upper airway obstruction requiring emergency tracheostomy. Biopsy showed a poorly differentiated carcinoma. Apparently no primary tumor was identified at that time. He received radical radiation therapy to the lower nasopharynx and cervical lymph nodes in Vietnam using parallel opposed fields to a dose of 40 Gy. This was followed by an anterior field to a total dose of 60 Gy, blocking the cord.

He remained well for 5 months when he developed loss of vision in the left eye and near total loss of vision in the right eye. He came to the United States and a CT scan of the head showed a 4 cm destructive lesion at the base of the skull extending superiorly to the optic chiasm. A right neck mass was noted and biopsy showed a poorly differentiated carcinoma consistent with a nasopharyngeal primary. Dr. Winkler, would you please present the imaging studies that were available to us at that time?

Peter Winkler, MD (Fellow, Neuro-Radiology)

The MRI images are the most informative (Fig. 1). They show a very large mass extending through the base of the skull from the nasopharynx. It fills the sphenoid sinus and the cavernous sinus, and extends to the posterior portions of each orbit, left more than right. The findings are consistent with non-Hodgkin's lymphoma (NHL) and rhabdomyosarcoma, both of which are common neoplasms in this age group. These findings are found in adults with nasopharyngeal carcinoma, of course. The pattern is consistent with that diagnosis, which is rare in children compared to the other two possibilities.

Dr. Werner-Wasik. The differential diagnosis is not long in children, and will be discussed in a little more detail in a moment. At this point, it would be interesting to review the results of the biopsy.

Antonia Uri, MD (Pediatric Pathologist)

The sample is a lymph node with sheets and nests of large cells with very prominent nuclei and many mitoses. The cells are undifferentiated, and in themselves are consistent with a large cell non-Hodgkin's lymphoma. However, there can be seen many areas where the lymph node architecture is entirely normal, making the possibility of metastatic involvement more likely. In fact, special stains for keratin are strongly positive in the tumor cells and not in the lymphocytes which appear normal. These special stains are extremely helpful, and we are confident that the proper diagnosis is secondary deposits from an epithelial carcinoma.

Joel Goldwein, MD (Pediatric Radiation Oncologist)

Do you have any estimate as to how often the diagnosis was missed or made in error before the advent of these special stains?

Dr. Uri. I don't have a good estimate but we would have called this metastatic carcinoma even without the keratin stain.

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Dr. Werner-Wasik. Because of near-blindness, he was started quickly on dexamethasone, fluorouracil (5-FU) and cisplatin, which resulted in some vision improvement in the right eye. Physical examination revealed mild xerostomia, friable mucosa in the anterior nasopharynx, but no obvious mass. There were II, III, and VI nerves palsies, well explained by the findings described by Dr. Winkler. Re-treatment with radiation therapy was offered. This would be possible because the new areas of involvement did not overlap with the fields used in Vietnam, except for the neck adenopathy.

The portals employed were two lateral opposed fields covering the nasopharyngeal tumor with a margin. The neck was not treated with the understanding that right neck adenopathy would be addressed later surgically.

The fractionation was initially the standard 180 cGy daily. This later was changed to hyperfractionation using 120 cGy twice daily to a higher total dose in the hope of achieving better local control. Three consecutive field reductions were used to protect the brain stem, spinal cord, and other normal tissues surrounding the tumor. The final dose to the nasopharynx was 6,900 cGy, of which 5,280 cGy was delivered with the hyperfractionated regimen.

Dr. Goldwein thought it would be helpful to monitor the response of the tumor in deciding on the eventual dose. Imaging studies were therefore repeated when 1,300 cGy had been delivered to see whether there was a decrease in the amount of involvement in the base of the skull. What did you find, Dr. Winkler?

Dr. Winkler. There had been a marked reduction in the size of the tumor after the combined chemotherapy and radiation therapy delivered up to that point (Fig. 2).

Dr. Goldwein. Another means of monitoring these patients is through the use of a flexible endoscope that was designed specifically to visualize the nasopharynx [1].

Giulio J. D'Angio, MD (Pediatric Radiation Oncologist)

Dr. Goldwein, why is this instrument so useful? Would you please tell us a little more about the device because it is unfamiliar to most pediatricians.

Dr. Goldwein. The flexible endoscope is a most valuable adjunct to the management of patients with head and neck cancers, and is very helpful in monitoring children. We have used the endoscope in children as young as 3-years-old because the fiberoptic arm is very flexible and small. It can be inserted easily after suitable nose drops have been instilled to provide local anesthesia and to shrink the nasal mucosal membranes. It is self-illuminating, and one can get an excellent view of the entire vault of the nasopharynx. Prior to this, even in adults, it was really difficult to get a good assessment of the local disease and its extent. In this case, for example, one could easily see that the bulging mass in the nasopharynx had disappeared, and that the mucosa looked normal.

Anna T. Meadows, MD (Pediatric Oncologist)

It must have been gratifying to see the prompt response, but how encouraged can one be under these sets of circumstances? There was extensive bony destruction and intracranial invasion, after all.

Dr. Goldwein. Nasopharyngeal carcinoma is perhaps unique among the epithelial cancers, because there is a good chance for cure despite fairly advanced local disease. Most of our experience, of course, comes from studies of adults, and perhaps we should now hear what Dr. Werner-Wasik has found in her search of the literature.

Dr. Werner-Wasik. This disease is so infrequent in children that it might be useful to review nasopharyngeal carcinoma in some depth. First the epidemiology is unusual. It is an uncommon tumor in the United States, but it is prevalent in China [2]. Males are affected more than females,and blacks more than whites. It is the only carcinoma of the head and neck region which is not strongly related to smoking. There is, however, a link to the Epstein-Barr virus (EBV). This is manifest by the elevated titres of immunological products that indicate exposure to EBV. Most of these patients demonstrate such elevated titres. The age distribution is bimodal. While 15–20% occur in patients younger than 30 years of age, it makes up only 1% of all malignant diseases in children; i.e., in patients under 16. The second peak is at ages 50–60 [3].

Nasopharyngeal carcinoma (NPC) arises from the epithelial lining of the nasopharynx and is, generally speaking, a squamous cell carcinoma although frank keratinization is not always a feature. We assume, however, that keratin stains would be positive in most if not all cases. Much more commonly, the cells are very undifferentiated, as in our patient, so that the cell of origin is difficult to identify. The diagnosis is made more by the "company the cell keeps," or by the use of special stains, as here.

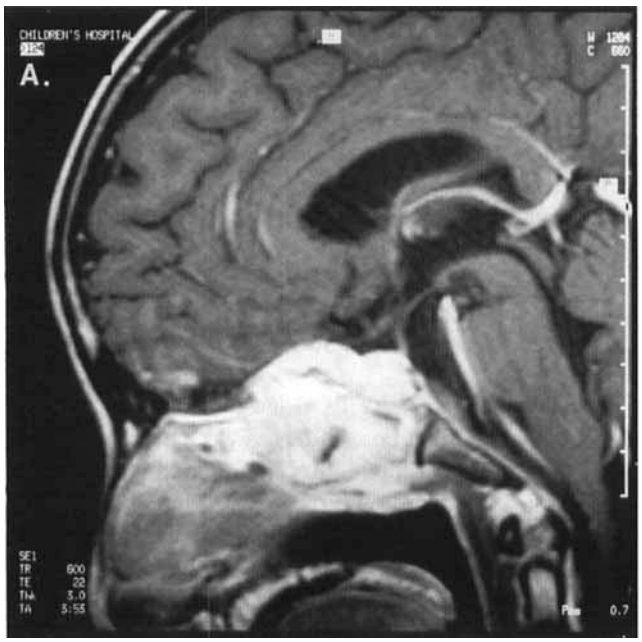
The differential diagnosis of a nasopharyngeal mass in a child includes rhabdomyosarcoma, usually embryonal in type, non-Hodgkin's lymphoma (rarely Hodgkin's disease), juvenile angiofibroma, which occurs almost exclusively in adolescent males, and finally nasopharyngeal carcinoma [1]. The World Health Organization (WHO) has classified nasopharyngeal carcinomas as follows:

WHO-1: Squamous cell carcinoma

WHO-2: Non-keratinizing carcinoma

WHO-3: Undifferentiated carcinoma

Lymphoepithelioma (carcinoma heavily infiltrated with lymphocytes) is included in the WHO-3 category. Some investigators believe it has higher rates of local control with radiation therapy, at the same time, however, being more prone to distant spread.



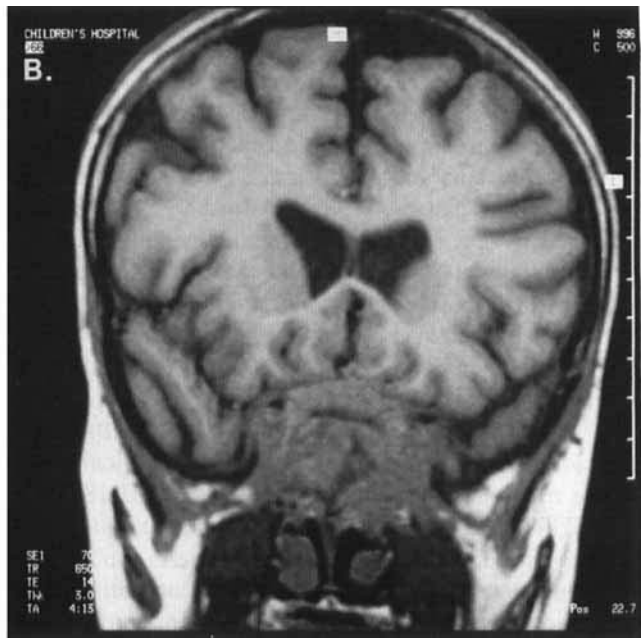


Fig. 1. Large nasopharyngeal tumor extending into the base of the skull. It fills and expands the sphenoid and cavernous sinuses. It has also invaded the apex of both orbits (not shown in these sections). The tumor produces a mass effect in the anterior cranial fossa, pushing up the planum sphenoidale. **A:** Midline sagittal T1-weighted MRI image. The large, vividly enhancing nasopharyngeal tumor occupies a large area including the superior clivus and the ethmoid bone. The displacement of the planum sphenoidale is shown. **B:** Nonenhanced coronal T1-weighted MRI through the cavernous sinus and nasopharynx.

Epstein-Barr virus is primarily associated with WHO types 2 and 3 nasopharyngeal carcinoma [3].

Tom et al. of our institution have described their experience with 29 children [1]. They point out that the differential diagnosis in children is helped to some extent by whether lymph nodes are or are not present. The diagnosis of NPC is almost always correct when there are enlarged neck nodes on one or both sides of the neck in association with a nasopharyngeal tumor. Rhabdomyosarcoma, by contrast, usually makes its presence known because of local manifestations; e.g., nasal voice, or protrusion of the tumor from the nostril, in the so-called sarcoma botryoides presentation. There often is a foul smell and the tumor may be seen extending into the oropharynx, depressing the soft palate. Lymph nodes may or may *not* be present; if they are, they are usually small by comparison to the findings in NPC. Also, younger children are usually affected by rhabdomyosarcoma. Juvenile angiofibroma is almost restricted to adolescent males, and lymph nodes except for inflammatory nodes are seldom present. The diagnosis is made because of brisk nose bleeds that can be exsanguinating. Finally, Hodgkin's and non-Hodgkin's disease are always distinct possibilities when uni- or bilateral neck nodes are present. Only biopsy will distinguish between a lymphomatous process and NPC.

It is frightening that so many different tumors can affect this relatively small anatomic space (Figs. 3,4). The nasopharynx is a 4 × 4 × 2.5 cm cuboidal space limited by the posterior choanae (anteriorly); the sphenoid sinus (superiorly); the clivus and the first two cervical vertebrae (posteriorly); the soft palate (inferiorly) and the Eustachian tube orifice, torus tubarius, and fossa of Rosenmüller (laterally).

NPC is staged according to the TNM system as follows: T1—tumor limited to one subsite of nasopharynx; T2—tumor invades two subsites of nasopharynx; T3—tumor invades nasal cavity or oropharynx; T4—tumor invades skull or cranial nerves [3]. Staging of the neck lymph nodes is similar to all other head and neck sites, with any lymph node larger than 3 cm being classified as at least N_2 disease and automatically qualifying the patient as Stage IV.

Survival is predicted best by T-stage, T1–T2 having the best prognosis. High N-stage identifies those at risk for distant metastases, and those with distant metastases at diagnosis have a poor outlook [4].

The signs and symptoms of NPC at presentation are almost always related to relatively advanced disease. Initial symptoms can be nasal obstruction, epistaxis, nasal discharge, headache, tinnitus, deafness, and otitis media [3,5]. These are relatively minor complaints, and are frequently ignored for some time until an asymptomatic neck mass becomes evident. This course is very frequent, and the incidence of neck node disease at presentation is 80–90%, 50% of cases having bilateral lymph nodal involvement. Unlike rhabdomyosarcoma, which tends to grow in an exophytic fashion, NPC grows by local infil-

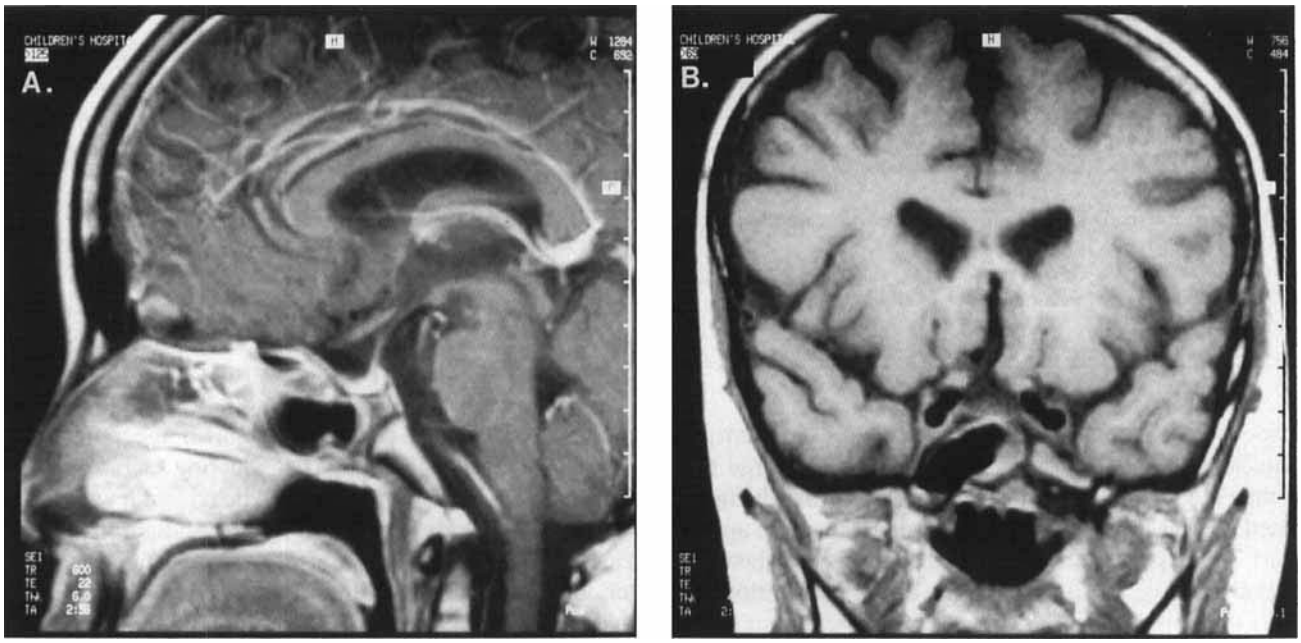


Fig. 2. Marked reduction in the size of the tumor after induction chemotherapy and 13 Gy of radiation therapy. **A:** Same section as in Figure 1A. Gross reduction of mass effect and tumor size. Residual enhancement might be due to treatment or mucosal reaction. Nodular areas of enhancement are no longer seen. **B:** Same section as in Figure 1B. The tumor is no longer visible on this section. The cavernous sinus has regained its original shape, the carotid arteries are no longer compressed. The sphenoid sinus is mostly aerated; some increased signal might be due to fluid or mucosal reaction.

tration. Indeed, the primary site may be difficult if not impossible to see, despite the presence of huge bilateral neck nodes. Also, because of the infiltrative pattern, it spreads through the normal foramina at the base of the brain as well as by direct bony extension (Fig. 1). The result is that cranial nerve involvement is present in about 25% of patients at diagnosis. The usual paths of extension are through the foramen lacerum and the foramen ovale to produce the so-called petrosphenoidal syndrome of Jacod [6]. The signs of this particular form of spread include unilateral ptosis because of third cranial nerve involvement, complete ophthalmoplegia (cranial nerves III, IV, and VI) with blindness (II) and pain or anesthesia in the first and second branches of the fifth nerve. Jaw deviation completes the picture. The other syndrome familiar to those dealing with head and neck cancer in adults is the retroparotid space syndrome of Villaret [6]. This includes dysphagia and aberrant taste sensations (IX, X), anesthesia of the palate, pharynx, and larynx (X), dropped shoulder (XI), tongue deviation (XII) and Horner's syndrome (cervical sympathetics). The tumors can spread in less devious ways; for example, directly anteriorly or downward to include the pterygoid plates leading to trismus [7]. Posterior spread to involve the prevertebral muscles has been recorded, leading to painful extension of the head [3]. Lateral growth can lead to obstruction of the Eustachian tubes with consequent otitis media and deafness [7].

The diagnostic work-up includes, of course, history and physical examination, to include direct and indirect nasopharyngoscopy either by mirror examination or fiberoptics. Imaging studies of the head and neck complete the evaluation of the tumor and its extensions. Biopsy is obviously always necessary for definitive diagnosis.

The prime mode of management has been radiation therapy. Before initiating roentgen irradiation, however, it is wise to obtain audiograms to establish the level of hearing. A dental consultation for initial evaluation is strongly advised, too. This is because the relatively high doses delivered to the salivary glands can lead to xerostomia such as was present in our patient. Xerostomia promotes the development of dental caries because of the decrease in salivary flow, and the differential suppression of the serous component of the saliva. Preventive mouth hygiene through the use of fluoride treatments and meticulous cleansing reduces the chance for caries [3].

Radiation therapy is directed to both the primary site and the neck even in patients without palpable nodal disease. A large initial field is necessary to include the nasopharynx proper with suitable margins [3]. The margins therefore extend to the posterior 2 cm or so of the nasal cavity, the posterior portion of the ethmoid sinus, the entire sphenoid sinus, the cavernous sinus, the base of the skull, the pterygoid fossa, the posterior third of the maxillary sinuses, the pharyngeal walls at the level of the mid-tonsilar fossae, and the retropharyngeal nodes and neck nodes on both sides. The fields must be extended to include the base of the skull more generously if there is

TABLE I. Late Effects of Irradiation for Nasopharyngeal Carcinoma

1. Xerostomia (45–60%) and increased risk of caries (10–15%)
2. Otitis-externa and media (15%)
3. Neck muscle fibrosis (approximately 10%)
4. Trismus—temporo-mandibular joint fibrosis (2–8%)
5. Soft tissue/bone necrosis (4–6%)
6. Transverse myelitis (1–4%; should be rare with cord doses of 45 Gy)
7. Cranial nerve palsy (1–5%)
8. Hypopituitarism (30% in one series in children, negligible in adults)
9. Retinopathy (incidence not clear, frequently asymptomatic)

evidence of cranial nerve involvement either through clinical examination or imaging studies. This large field is then reduced in size after 45–50 Gy to bring the implicated volumes (nasopharynx and palpable nodes) up to at least 70 Gy [3,8,9]. The lower neck and supraclavicular regions receive 50 Gy through the use of an anterior field with the spinal cord and brain stem blocked such that these structures do not receive more than 45 Gy and the optic chiasm not more than 50 Gy.

The results of such treatment in children is difficult to ascertain. In brief, 5-year survival in a combined review by the M.D. Anderson Hospital and the Stanford Medical Center [10] suggested a survival of about 50%. A similar figure was reported by the Children's Cancer Study Group in 1981 [11]. The prognosis is directly related to the extent of the primary tumor: those with T1–T2 tumors have a 75% 5-year survival; this drops to 37% expectancy for patients with T3–T4 neoplasms. Aggressive treatment of this kind yields better local control and survival for the so-called lymphoepithelioma type of tumor (by 15–20 percentage points). Local control of disease is achieved in 90% of patients with T1/T2 lesions; this drops to 30–60% for T3/T4 disease [3,9].

Intensive treatment of the kind described exacts a price, of course, in terms of late effects [3,5,11,14]. These are listed in Table I.

Jeffrey Silber, MD, PhD (Pediatric Oncologist)

Some other untoward events such as the advent of second malignant neoplasms (SMNs), effects on growth and development, and the incidence of cataracts need to be mentioned.

Dr. Goldwein. Let me say that second malignant neoplasms are always possible but appear to be uncommon in the survivors of NPC. Growth and development can be affected directly, of course. The severity of these effects is proportional to the dose and inversely related to the age as a rough rule of thumb. Indirect effects also must be remembered when the pituitary gland is necessarily included in the beam. Cataracts are rare because the beam is well posterior to the lens in most patients with this disease.

Dr. D'Angio. The high doses delivered may explain the relatively low frequency of second malignant neoplasms. Both in experimental systems and in clinical experience, it has been noted that the frequency of SMNs rises with increasing dose up to a certain point. After that, the frequency falls; at least, it does so in animal systems. The postulated reason is that there are fewer normal cells surviving in the high-dose regions and therefore fewer are subject to irradiation oncogenesis.

Dr. Werner-Wasik. Finally, the role of chemotherapy needs to be discussed. It remains controversial. Several retrospective trials [15,16] suggest that better results are achieved in adults by combined modality care, but only a randomized clinical trial will establish the point. The Southwest Oncology Group is conducting such a randomized trial, and their results will be viewed with great interest. The study conducted by the Radiation Therapy Oncology Group (RTOG), also in adults, suggests a better outcome when cisplatin is used together with radiation therapy. Historical controls were used in the RTOG trial, and there was a better overall result for Stage IV patients at 4 years (62 vs. 27%) [17]. The results are clouded, however, because there were more good performance score patients in the combined group.

I have reviewed the results obtained in six children treated in our department who received combined chemo-radiotherapy in the period 1988 through 1993. Their ages ranged from 12 to 17 years (median 14). There were five boys and one girl, and all were Stage IV at the time of diagnosis. With a median follow-up of 3.23 years, five of the six patients are alive and free of disease. One child relapsed distantly and died despite salvage chemotherapy even though the primary disease remained under control. All six received induction chemotherapy either with 2 cycles of fluorouracil and cisplatin (five patients), or cyclophosphamide/cisplatin (one patient). Four of the six children were treated with standard fractionated radiation therapy to total doses of 61.2, 69, 72.2, and 70.2 Gy. (The remaining two received hyperfractionated radiation therapy going to doses of 69 Gy and 74.4 Gy.)

The actuarial survival at 5 years is 83%, and good local control was achieved in all six children. These results are encouraging, of course, especially since all six were Stage IV at diagnosis. More patients and longer follow-up are clearly needed nonetheless, before firm conclusions can be drawn.

It is interesting that re-treatment with radiation therapy (RT) after failure of primary RT is feasible, and the salvage rate is apparently good [3].

Beverly Lange, MD (Pediatric Oncologist)

It is surprising that effective doses of RT can be given for salvage purposes after such aggressive primary management. How do you do that?

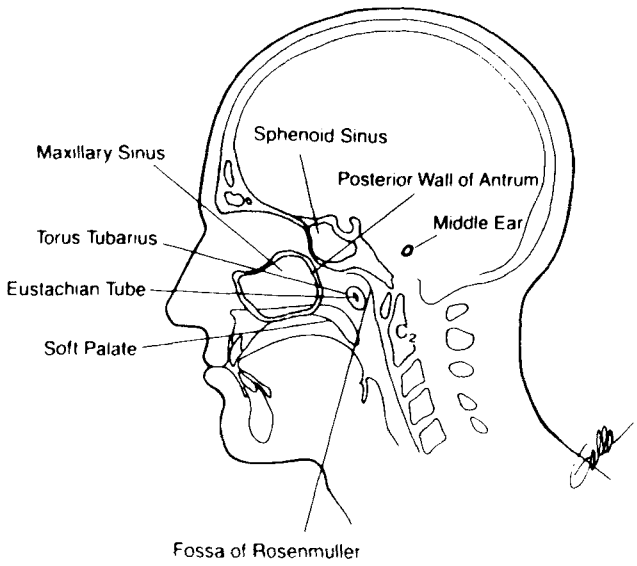


Fig. 3. Anatomic structures adjacent to the nasopharynx. Note position of fossa of Rosenmüller, torus, and Eustachian tube. (Reproduced with permission from Wang CC: "Radiation Therapy for Head and Neck Neoplasms," 2nd Ed. St. Louis, MO: The C.V. Mosby Company, 1990.)

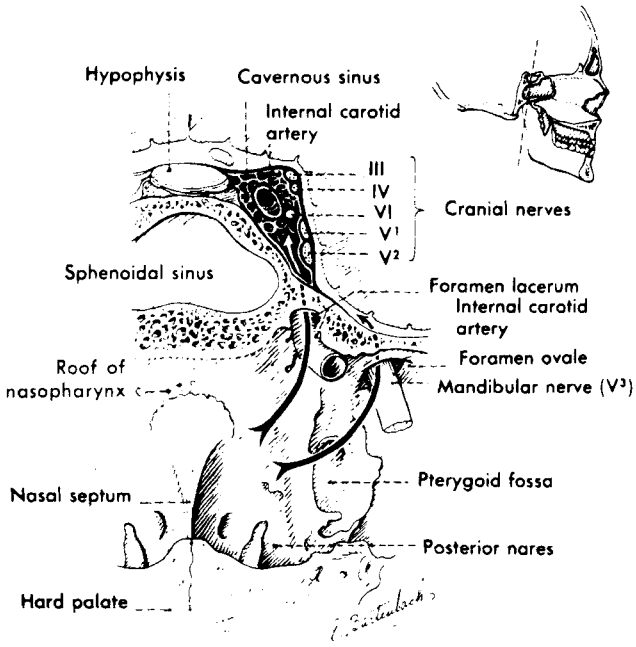


Fig. 4. Routes of spread of nasopharyngeal carcinoma through foramen lacerum and foramen ovale. (Reproduced with permission from Moss WT: "Moss' Radiation Oncology: Rationale, Technique, Results." 7th Ed. St. Louis, MO: The C.V. Mosby Company, 1994.)

Dr. Goldwein. Re-treatment is only considered when the area to be treated is small. The dose from external beams can be supplemented by the use of brachytherapy techniques. In patients suitable for this approach, salvage rates of about 30% have been reported.

Dr. Werner-Wasik. In summary, NPC can be managed successfully with high-precision, high-dose radiation therapy. The role of surgery is limited to biopsy and perhaps the removal of residual neck masses after RT. NPC can be considered one of the radio-curable carcinomas, along with those of the skin, larynx, and cervix. In low-stage lesions, the 5-year survival rate for NPC is 70–80% after radiation therapy of the type described. Involvement of the bone and of the cranial nerves does not necessarily preclude the possibility of a cure, although the chances for success are reduced by approximately 50%.

ADDENDUM

The index patient is free of disease 1 year after completion of 6,900 cGy given to the nasopharynx. He has minimal vision in the right eye and no vision in the left eye. There are no other neurological deficits.

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SERIES EDITOR'S NOTE

Nasopharynx is basically polyglot (Greek: many languages) being formed from the Latin: *nasus* = nose + *pharynx* which was adapted from the Greek term for throat. It nonetheless conveys the appropriate mental picture, as does *pterygoid* or wing-like from the Greek *pteron* = wing. *Clivus* (Latin: slope) also is a fitting term for that portion of the *sphenoid* bone at the base of the skull [*sphenoid:* Greek *sphen* (wedge) + *eidos* (form) = wedge-shaped] that extends downward from the region of the *sella turcica* (Latin = Turkish saddle) to articulate with the occipital bone (*occiput* = Middle English from Latin: *ob-* = against + *caput* = head).

Torus tubarious is very descriptive of the local anatomy [Latin = rounded swelling of the (Eustachian) tube].

Eustachius (1524–1574) is the Latinized form for Bartolomeo Eustachio, Professor of Pathology in Rome at the precursor of "La Sapienza," as the University of Rome has come to be known. He compiled an atlas of anatomical plates in the mid-1500s, and was the first to describe the adrenal gland and other important structures. His name has been associated mostly with the *tuba auditiva,* (Eustachian tube) which is perhaps the least important of his discoveries.

Johann Friedrich Horner (1831–1866) was a Swiss ophthalmologist who became professor of that specialty in Zurick after studies abroad. He not only identified "his" cervical sympathetic syndrome (narrowed palpebral fissure, meois, enophthalmos, and decreased sweating) but also established that color blindness was sex-linked in inheritance. It is interesting that it was another Horner (William Edmonds H.), an American anatomist who lived from 1793 to 1853 for whom the ocular muscle is named.

Johann Christian Rosenmüller (1779–1820) was a German anatomist whose detailed studies led to the identification of the *epoöphoron,* a vestigial structure; and the deep inguinal lymph nodes. He also described the *plica lacrimalis,* a fold at the distal opening of the lacrimal duct which is also ascribed to Joseph Ritter von Artha Hasner (1819–1892), a Prague ophthalmologist. Rosenmüller is best remembered, however, because of the *recessus pharyngeus,* which he also described; i.e., the fossa of Rosenmüller.

Maurice Jacod (1888–?) was a French neurologist who, in 1921, described the petrosphenoid triad that bears his name. The triad consists of optic atrophy, total ophthalmophagia, and trigeminal neuralgia secondary to involvement of cranial nerves II-VI.

Maurice Villaret (1877–1946) also was French. Artistically inclined, his main medical interests were in rehabilitation and related fields including the therapeutic value of spas. Another interest was in vascular lesions of the brain. He was an attentive observer of the clinical pictures presented by his patients and described the unilateral paralysis of cranial nerves IX-XII and the cervical sympathetics caused by tumor extension behind and deep to the parotid (Greek: *para-* + *tous:* near the ear) gland.

Michael Anthony Epstein (1921–) and Yvonne M. Barr (1932–), working in London, found the EB virus as it has come to be known, through studies of Burkitt's lymphoma. A cell line was established, and electron microscopic examinations revealed the virus.

Dennis Parsons Burkitt (1911–1993), was an Ulsterman who received his degree from Dublin University. He was a surgeon in the colonial service in Uganda, where he identified the lymphomatous process that bears his name.

Much of the early seminal work in the radiation therapy of head and neck cancers was conducted in France. It was there that Claudius François Regaud (1870–1940), Henri Coutard (1876–1950), and Antoine Marcelin Lacassagne (1884–1971) established fractionation of dose and other techniques still in use today. These master clinicians emphasized the need for close examination of patients both at diagnosis and during therapy. Neurologic deficits, when present in patients with nasopharyngeal carcinoma, identified the extent of disease and directed the placement of fields to include the implicated anatomic areas. These patterns are known through their eponymic syndromes.